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ORIGINAL RESEARCH

Expression and Significance of PI3K p85α and p53 Protein in Colorectal Cancer Tissues

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Aim: To evaluate the expression of PI3K p85α and p53 proteins in colorectal cancer (CRC) tissues, investigate their roles in carcinogenesis and progression, and analyze their associations with clinicopathological characteristics and patient prognosis.

Methods: Immunohistochemistry was used to assess the expression of PI3K p85α and p53 proteins in CRC tissues and matched paracancerous mucosa from 267 patients. The associations between protein expression and clinicopathological characteristics were analyzed. Follow-up data were evaluated using univariate Kaplan–Meier survival analysis and multivariate Cox regression analysis.

Results: The positive rate of PI3K p85α was significantly higher in CRC tissues than in paracancerous mucosa (80.2% vs 17.6%, P<0.001) and was associated with clinical stage (χ^2=5.261, P=0.022). p53 expression profiles were markedly different between CRC and normal tissues, with a significantly higher rate of p53 overexpression in CRC (62.9% vs 0%, P<0.001). Importantly, both negative and high p53 expression were associated with a higher incidence of lymph node metastasis (P<0.05). In survival analysis, clinical stage, tumor differentiation, and PI3K p85α expression were identified as independent prognostic factors for CRC patients (P<0.05).

Conclusion: PI3K p85α and p53 are implicated in CRC development and progression. The detection of these proteins offers clinical value for early diagnosis and predicting tumor behavior, while PI3K p85α expression may serve as a valuable biomarker for prognostic assessment in CRC.

Keywords: colorectal carcinoma, PI3K p85α, p53, immunohistochemistry

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy worldwide, accounting for approximately 10% of all new cancer cases and 9.4% of cancer-related deaths annually, making it the second leading cause of cancer mortality.[1] Although significant progress has been made in early screening and therapeutic strategies for CRC, its incidence remains high, and survival outcomes for many patients remain suboptimal. Therefore, there is an urgent need to identify novel biomarkers to improve early detection, prognostic assessment, and clinical management of CRC.

The development and progression of CRC involve a multistep process driven by multiple genetic and environmental factors, including alterations in genes such as TP53. The wild-type TP53 gene encodes p53, a nuclear tumor suppressor protein that plays a critical role in inhibiting tumor growth and preventing malignant transformation. Under normal, non-stress conditions, p53 is maintained at low intracellular levels through continuous proteasomal degradation mediated by the E3 ubiquitin ligase MDM2, its primary negative regulator.[2] Following TP53 mutation, the resulting p53 protein often acquires an extended half-life and increased stability, leading to its abnormal accumulation within the nucleus. Such mutations typically abrogate the tumor-suppressive functions of p53 and may even confer oncogenic gain-of-function properties. TP53 mutation is one of the most frequent genetic alterations in human cancers and is regarded as a key driver event in the development of multiple tumor types.[3]

Phosphatidylinositol 3-kinase (PI3K) is a specialized class of lipid kinases that phosphorylates phosphatidylinositol lipids, thereby propagating intracellular signaling cascades. PI3K plays a critical role in regulating diverse cellular processes, including cell proliferation, differentiation, apoptosis, and intercellular adhesion.[4] Protein kinase B (AKT) serves as a crucial downstream effector of PI3K signaling. The PI3K/AKT pathway participates in cellular malignant

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transformation processes and promotes tumor cell proliferation, invasion, and metastasis. Aberrant activation of PI3K/AKT constitutes a key mechanism regulating multidrug resistance, with PI3K recognized as a significant contributor to chemotherapy resistance in cancer treatment.[5] As an upstream signaling molecule in the PI3K/AKT pathway, PI3K consists of a p85 regulatory subunit and a p110 catalytic subunit. The p85 regulatory subunit is essential for stabilizing the p110 catalytic subunit, facilitating its recruitment, and activating PI3K. Among PI3K family members, p85α represents the most abundantly expressed regulatory subunit.[6] In addition to modulating PI3K activity through its interaction with p110, p85α itself also exerts important biological functions in CRC cell proliferation. Previous studies have shown that targeted silencing of PI3K p85α via RNA interference can effectively inhibit cell proliferation, induce G1-phase cell-cycle arrest, and enhance the sensitivity of CRC cells to 5-fluorouracil-induced apoptosis.[7,8] However, the differential expression patterns of PI3K p85α during colorectal carcinogenesis and progression remain poorly understood. Moreover, studies examining the potential correlation between PI3K p85α and p53 expression in CRC tissues, as well as their clinical prognostic significance, are limited.

To address these questions, we employed immunohistochemistry to assess the expression of PI3K p85α and p53 proteins in CRC tissues and corresponding paracancerous intestinal mucosa. We analyzed their differential expression between tissue types and examined associations with clinicopathological features of CRC patients. Additionally, we explored the potential roles of PI3K p85α and p53 in CRC pathogenesis and progression, as well as their relationships with patient prognosis.

Materials and Methods

Data Collection

CRC and paracancerous intestinal mucosa paraffin-embedded tissue specimens, surgically resected between December 2014 and August 2024 from the Affiliated People's Hospital of Ningbo University (APHNU) and Guizhou Provincial People's Hospital (GPPH), were selected for this study. All specimens were independently evaluated by two pathologists with over 10 years of clinical experience for diagnosis and assessment of tumor differentiation. Cases with discrepant assessments were referred to a senior pathological expert with more than 15 years of clinical experience for final adjudication. All specimens were clinically staged according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition. This study was approved by the Ethics Committee of APHNU (Approval No. 2024–068) and the Ethics Committee of GPPH (Approval No. 2019–63), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective study design and the use of de-identified patient data.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) postoperative pathological confirmation of diagnosis; (2) no history of radiotherapy, chemotherapy, or biological therapy prior to surgery; and (3) availability of complete clinicopathological data. Exclusion criteria: (1) presence of critical comorbidities such as severe cardiovascular disease, concurrent malignancies in other organs, and severe chronic obstructive pulmonary disease; and (2) a family history of CRC in first- or second-degree relatives.

Immunohistochemistry

Consecutive 4-μm sections were prepared from formalin-fixed, paraffin-embedded (FFPE) tissue blocks obtained from postoperative colorectal cancer patients. For each patient, a single FFPE tissue block was selected. Immunohistochemical detection of PI3K p85α and p53 proteins was performed on consecutive sections from the same tissue block, ensuring consistency in the analyzed tissue regions for the two targets. Immunohistochemistry was performed according to the instructions of the SP kit.[9] Both PI3K p85α and p53 antibody incubations were preceded by high-pressure heat-induced antigen retrieval. Known positive cancer tissue samples served as positive controls, while phosphate-buffered saline (PBS) replaced the primary antibody for blank controls. The antibodies used included: concentrated rabbit anti-human PI3K p85α polyclonal antibody (clone N2C1, dilution 1:3200, GeneTex, USA), and concentrated mouse anti-human p53

monoclonal antibody (clone DO-7, dilution 1:100, Zhongshan Golden Bridge Biotechnology, China). Both the DAB detection kit and SP staining kit were obtained from Zhongshan Golden Bridge Biotechnology (China).

Immunohistochemical staining results were independently evaluated by two senior pathologists. In cases of disagreement, a third senior pathology expert was consulted for arbitration to ensure diagnostic reliability and accuracy. PI3K p85α protein expression was primarily localized in the cytoplasm. Assessment was based on two independent scoring factors:[10] staining intensity (0 = none, 1 = light yellow, 2 = brownish yellow, 3 = tan) and staining area (0 = 0%, 1 = ≤25%, 2 = 26%-50%, 3 = 51%-75%, 4 = >75%). The final score was calculated by multiplying these two factors, with scores <3 considered negative expression and scores ≥3 considered positive expression. p53 protein expression was considered positive when brownish granular staining was observed in the nucleus. Evaluation followed methods described by Oh et al[11] and Rachmawati et al[12] based on two independent scoring factors: staining intensity (0 = none, 1 = light yellow, 2 = brownish yellow, 3 = tan) and staining area (0 = 0%, 1 = <50%, 2 = ≥50%). The product of these scores was interpreted as follows: 0 = negative, 1–3 = low expression, and 4–6 = high expression.

Statistical Analysis

Statistical analyses were conducted using SPSS version 25.0. Differences in expression rates between groups were assessed using the χ^2-test, and correlations were evaluated with Spearman's rank correlation. Survival analyses were performed using the Kaplan-Meier method with the Log rank test, followed by multivariate Cox regression analysis. A P value < 0.05 was considered statistically significant.

Results

Data Characteristics

This study included a total of 267 paraffin-embedded tissue specimens of CRC and paracancerous intestinal mucosa (171 males and 96 females, age range: 23–89 years, median age: 62 years). Among these, 143 specimens were obtained from the APHNU, and 124 specimens were from GPPH. Regarding tumor differentiation: 62 cases (23.2%) were poorly differentiated, 187 cases (70.1%) were moderately differentiated, and 18 cases (6.7%) were well-differentiated. According to clinical staging: 12 cases (4.5%) were stage I, 39 cases (14.6%) were stage II, 106 cases (39.7%) were stage III, and 110 cases (41.2%) were stage IV.

PI3K p85α and p53 Protein Expression in CRC and Paracancerous Intestinal Mucosa Tissues

PI3K p85α positivity in CRC tissues was primarily localized to the cytoplasm, appearing as light yellow, brownish-yellow, or tan. In paracancerous intestinal mucosa tissue, faint cytoplasmic staining was observed in a small number of cells, appearing pale yellow; according to the interpretation criteria for PI3K p85α, these were classified as negative. Representative immunohistochemical staining results showing negative PI3K p85α expression in paracancerous intestinal mucosa, alongside positive and negative PI3K p85α expression in CRC tissue, are presented in Figure 1. PI3K p85α protein expression was significantly higher in CRC tissues than in paracancerous intestinal mucosa ($\chi^2 = 209.012$, $P < 0.001$) (Table 1).

p53-positive nuclei exhibited immunostaining, whereas negative nuclei showed no staining. (Figure 2A–D). In CRC and paracancerous intestinal mucosa tissues, the rates of negative, low, and high p53 expression were 20.6% (55/267), 16.5% (44/267), and 62.9% (168/267), and 46.8% (125/267), 53.2% (142/267), and 0% (0/267), respectively. The high-expression rate of p53 in CRC (62.9%, 168/267) was significantly higher than that in paracancerous intestinal mucosa (0%, 0/267; $P < 0.05$) (Table 1). The significantly higher rate of high p53 expression in CRC (62.9%), which was absent in adjacent mucosa, suggests the prevalent accumulation of mutant p53 protein in tumors. Conversely, the significantly higher rate of low p53 expression in adjacent mucosa (53.2%) indicates that this state is characteristic of normal tissue.

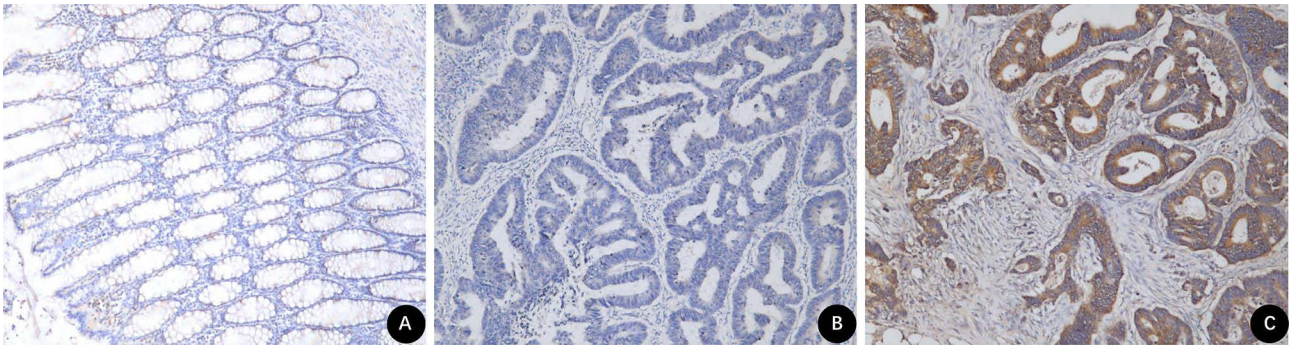

Figure 1 Expression of PI3K p85α protein in colorectal cancer and paracancerous intestinal mucosa tissues (100×magnification). (**A**) Negative PI3K p85α expression in paracancerous intestinal mucosa tissue. (**B**) Negative PI3K p85α expression in colorectal cancer tissue. (**C**) Positive PI3K p85α expression in colorectal cancer tissue.

Association Between PI3K p85α and p53 Protein Expression with Clinicopathological Characteristics of CRC Patients

PI3K p85α protein expression showed a significant correlation with clinical stage in CRC patients (χ^2=5.261, P<0.05). p53 protein expression demonstrated no significant correlation with patient age, gender, tumor differentiation grade, or clinical stage (all P>0.05), but was significantly associated with lymph node metastasis (χ^2=6.063, P=0.048) (Table 2).

Correlation Between PI3K p85α and p53 Protein Expression in CRC Tissue

No statistically significant correlation was observed between PI3K p85α and p53 protein expression in CRC tissue (r = −0.055, P = 0.283) (Table 3).

Association Between PI3K p85α and p53 Protein Expression with Survival Prognosis in CRC Patients

Follow-up was completed in August 2025, with valid follow-up data obtained for 237 patients, yielding a follow-up rate of 88.8% (237/267). The follow-up duration ranged from 1 to 116 months. During this period, 108 patients (45.6%) died and 129 (54.4%) remained alive. Kaplan–Meier survival analysis showed overall survival rates of 89.9% at 1 year, 79.2% at 2 years, 68.1% at 3 years, and 52.4% at 5 years. Univariate survival analysis was performed for age (>65 years vs ≤65 years), gender (male vs female), clinical stage (I, II, III, IV), tumor differentiation (well-differentiated, moderately-differentiated, poorly-differentiated groups), lymph node metastasis (present vs absent), PI3K p85α expression (negative vs positive groups), and p53 protein expression (negative, low-expression, high-expression groups). The analysis demonstrated that clinical stage, tumor differentiation, lymph node metastasis, and PI3K p85α expression were significantly associated with prognosis (Figure 3 and Table 4). Patients with stage I and II diseases exhibited longer survival times than those with stage III and IV diseases (χ^2=64.466, P<0.001) (Figure 3A). The well- and moderately-differentiated groups showed longer survival than the poorly-differentiated group (χ^2=13.638, P=0.001) (Figure 3B). Patients without lymph node metastasis survived longer than those with metastasis (χ^2=11.557, P=0.001) (Figure 3C).

Table 1 Expression of PI3K p85α and p53 Proteins in Different Types of Colorectal Tissues

Tissue Type	Number of Cases	PI3K p85α		χ^2	*P1*	p53			χ^2	*P2*
		Positive	Negative			Negative	Low Expression	High Expression		
Paracancerous intestinal mucosa	267	47	220	209.012	0.000[a]	125	142	0	246.857	0.000[a]
Colorectal cancer	267	214	53			55	44	168		

Notes: [a]P<0.05. *P1* value was calculated using the χ^2 test to compare PI3K p85α expression between colorectal cancer and paracancerous intestinal mucosa. *P2* value was calculated using the χ^2 test to compare p53 expression between colorectal cancer and paracancerous intestinal mucosa.

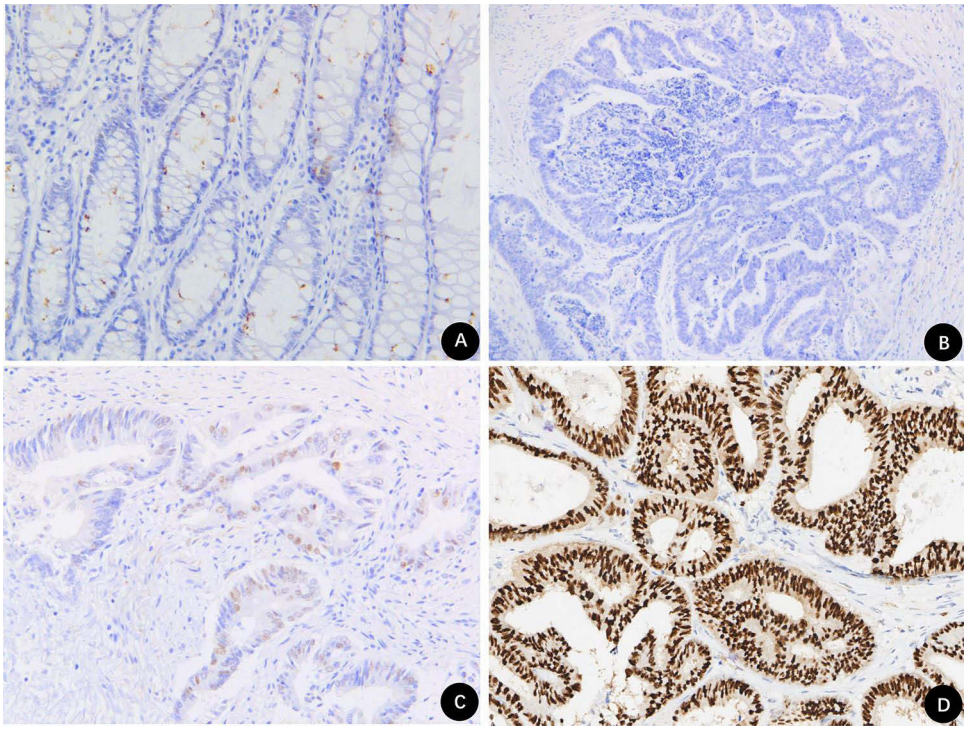

Figure 2 Expression of p53 protein in colorectal cancer and paracancerous intestinal mucosa tissues (200×magnification). (**A**) Negative p53 expression in paracancerous intestinal mucosa tissue. (**B**) Negative p53 expression in colorectal cancer tissue. (**C**) Low expression of p53 in colorectal cancer tissue. (**D**) High expression of p53 in colorectal cancer tissue.

The PI3K p85α negative group demonstrated longer survival than the positive group (χ^2=7.612, P=0.006) (Figure 3D). No significant correlation was observed between p53 protein expression and patient survival time (P>0.05) (Figure 3E). Multivariate Cox regression analysis incorporating age, gender, clinical stage, tumor differentiation status, lymph node

Table 2 Association of PI3K p85α and p53 Protein Expression with Clinicopathological Characteristics in Patients with Colorectal Cancer

Clinicopathological Characteristics	Number of cases	PI3K p85α		χ^2	*P1*	p53			χ^2	*P2*
		Positive	Negative			Negative	Low Expression	High Expression		
Age (years)										
≤65	166	137	29	1.192	0.275	40	25	101	3.443	0.179
>65	101	77	24			15	19	67		
Sex										
Male	171	140	31	0.886	0.347	36	28	107	0.060	0.971
Female	96	74	22			19	16	61		
Clinical stage										
I+II	51	35	16	5.261	0.022[a]	9	11	31	1.303	0.521
III+IV	216	179	37			46	33	137		
Degree of tumor differentiation										
High and moderate	205	167	38	0.957	0.328	37	33	135	4.072	0.131
Low	62	47	15			18	11	33		
Lymph node metastasis										
Yes	196	161	35	1.840	0.175	44	26	126	6.063	0.048[a]
No	71	53	18			11	18	42		

Notes: [a]*P*<0.05. *P1* value was calculated using the χ2 test between positive and negative PI3K p85α protein expression. *P2* value was calculated using the χ2 test among low expression, high expression, and negative p53 protein expression.

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Table 3 Correlation Between PI3K p85α and p53 Protein Expression in Colorectal Cancer Tissues

PI3K p85α	Number of Cases	p53			*r*	*P*
		Negative	Low Expression	High Expression		
Negative	53	7	12	34	−0.055	0.283
Positive	214	48	32	134		

Note: *r* and *P* represent the correlation coefficient and *P* value, respectively, between PI3K p85α and p53 protein expression (Spearman rank correlation).

metastasis, and PI3K p85α and p53 protein expression revealed that clinical stage, tumor differentiation status, and PI3K p85α protein expression were independent prognostic factors for postoperative survival in CRC patients (RR=3.430, P<0.001; RR=0.467, P<0.001; RR=2.029, P=0.026) (Table 4).

Discussion

PI3K plays a crucial role in cellular proliferation, differentiation, apoptosis, and aging. The PI3K/AKT signaling pathway contributes to malignant transformation by promoting tumor cell proliferation, invasion, and metastasis,[13,14] nd acts as a key driver of therapeutic resistance and disease progression in cancer.[15] Although recent studies have confirmed that elevated PI3K expression is associated with the development and progression of various malignancies—including lung, pancreatic, breast, and ovarian cancers—its relationship with CRC remains inadequately characterized.[15] p85α is the most abundantly expressed regulatory subunit of the PI3K family.[6] Our results demonstrate that the positivity rate for PI3K p85α protein was 80.2% in CRC tissues, significantly higher than the 17.6% observed in paracancerous intestinal mucosa. This suggests that PI3K p85α expression is upregulated during colorectal carcinogenesis and may play a role in the early prediction of malignant transformation. These findings are consistent with those reported by Benistant et al[16] who detected high levels of PI3K protein expression in the cytoplasm of tumor cells from colorectal, bladder, and ovarian cancers using immunohistochemistry. Furthermore, this study revealed that PI3K p85α expression correlates with clinicopathological stage, with higher positivity rates observed in more advanced stages. These results indicate that PI3K p85α protein plays an important role in the initiation, invasion, and metastasis of CRC and may serve as a valuable indicator for assessing disease progression.

The wild-type TP53 gene encodes the nuclear protein p53, a potent tumor suppressor that inhibits tumor growth and prevents tumor initiation and progression. This protein also functions as a transcription factor that activates numerous target genes involved in cell cycle arrest, apoptosis, and DNA repair.[17–20] Additionally, p53 can exert anti-proliferative effects through transcription-independent mechanisms.[20,21] Studies have reported that p53 influences nearly all cellular organelles, including mitochondria, lysosomes, and the endoplasmic reticulum.[22–25] In normal, non-stressed cells, p53 protein levels remain low due to constitutive proteasomal degradation mediated by the E3 ubiquitin ligase MDM2, its primary inhibitor.[2] Following mutation of the TP53 gene, the encoded p53 protein loses its tumor-suppressive activity and can become oncogenic. This represents the most common single-gene alteration in human cancers and is considered a driver event in numerous tumor types. Accumulating evidence indicates that beyond loss of tumor suppressor function, certain p53 mutants acquire novel gain-of-function activities that further promote tumorigenesis. Notably, although mutant p53 loses its tumor-suppressive capacity, it can still co-opt other transcription factors to drive the expression of tumor-promoting genes.[26] Unlike other tumor suppressor genes identified to date, cancer-associated TP53 mutations predominantly consist of missense mutations resulting from single amino acid substitutions.[27–29] Approximately 80% of TP53 mutations are missense mutations occurring within the central sequence-specific DNA-binding domain. The resulting mutant p53 proteins accumulate to high levels in cancer cells; consequently, strong p53 immunostaining in tumor sections is considered a reliable indicator of missense mutations. In this study, immunohistochemical analysis revealed negative or low p53 expression in paracancerous intestinal mucosa, while CRC tissues showed a significantly higher rate of strong p53 expression (62.9%) compared to normal mucosa (0%). This suggests that upregulation of p53 expression plays an important role in the progression from normal colorectal mucosa to carcinoma, indicating that detection of p53 protein may have value for predicting early carcinogenesis and facilitating early diagnosis.

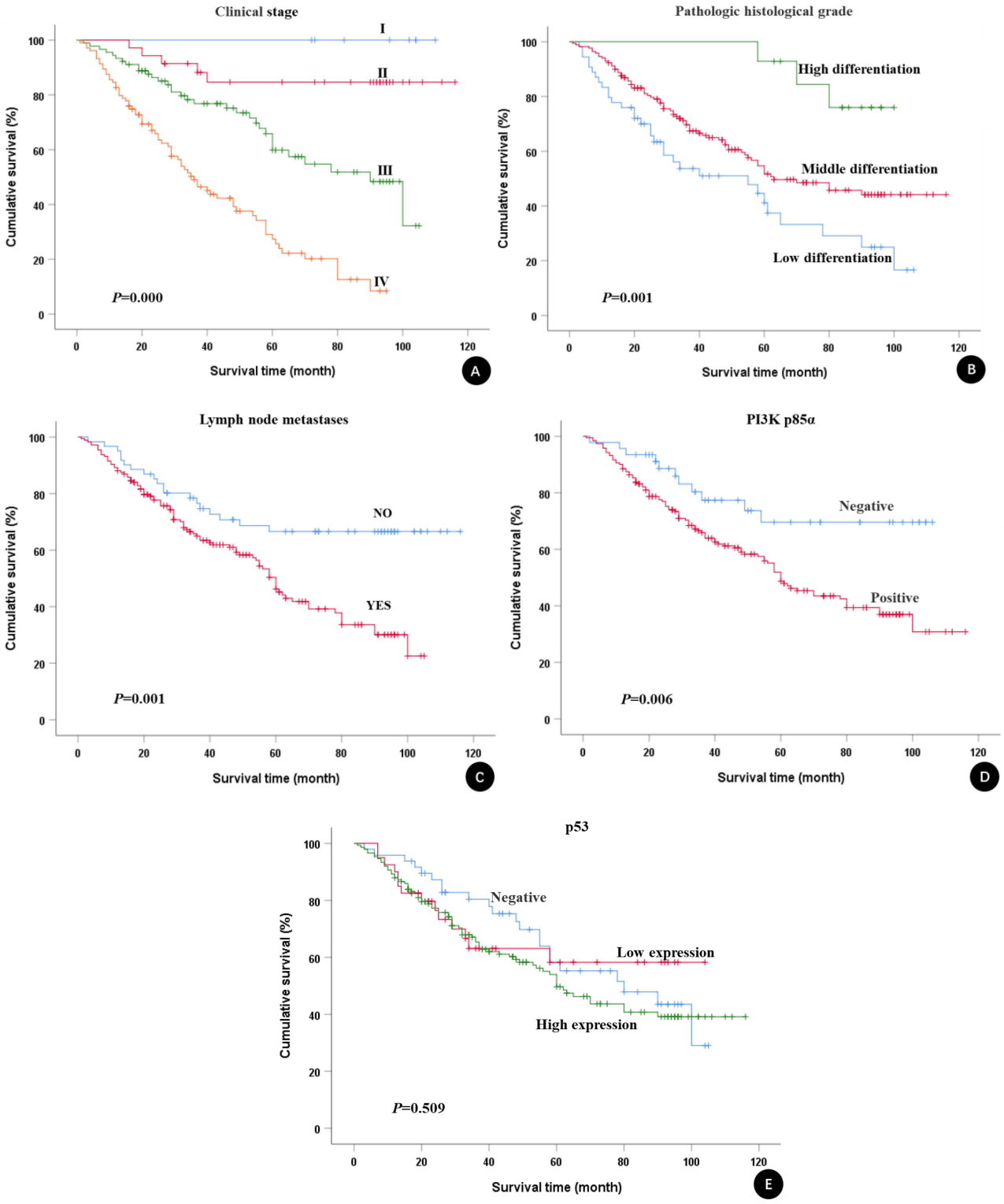

Figure 3 The relationship between clinicopathological parameters, PI3K p85α and p53 protein expression and the survival time of CRC patients. (**A**) The effect of the clinical stage on the survival time. (**B**) The effect of the degree of tumor differentiation on the survival time. (**C**) The effect of lymph node metastasis on the survival time. (**D**) The effect of PI3K p85α protein expression on the survival time. (**E**) The effect of p53 protein expression on the survival time.

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Table 4 Univariate and Multivariate Cox Regression Analyses of Patients with Colorectal Cancer

Factor	Univariate Analysis			Multivariate Analysis		
	RR	95% CI	P	RR	95% CI	P
Age (≤65 years old and >65 years old)	1.337	0.908~1.969	0.141	—	—	—
Sex (male and female)	0.765	0.509~1.149	0.197	—	—	—
Clinical stage (I, II, III, and IV)	3.194	2.321~4.394	0.000[a]	3.430	2.439~4.823	0.000[a]
Degree of tumor differentiation (low, moderate, and high)	0.519	0.366~0.737	0.000[a]	0.467	0.324~0.671	0.000[a]
Lymph node metastasis (yes and no)	2.315	1.404~3.819	0.001[a]	—	—	—
PI3K p85α protein expression (positive and negative)	2.338	1.251~4.367	0.008[a]	2.029	1.086~3.789	0.026[a]
p53 protein expression (negative, low, and high)	1.198	0.683~2.102	0.528	—	—	—

Note: [a]P<0.05.
Abbreviations: RR, relative risk; CI, confidence interval.

Oh et al[11] compared immunohistochemical results of p53 protein in CRC with targeted exon sequencing data, confirming a significant correlation between p53 protein expression and TP53 genetic status. While strong p53 expression was associated with missense mutations, most cases with negative p53 expression exhibited nonsense mutations. This suggests that CRC patients with low p53 protein expression are more likely to harbor wild-type TP53 genes. Therefore, this study employed a three-tier grouping model (negative, low expression, and high expression groups) based on p53 protein expression patterns. We found that both negative and high p53 expression (grouped as mutant pattern) were significantly associated with lymph node metastasis, indicating that mutant-type p53 expression patterns (either negative or high) enhance the invasive and metastatic potential of CRC. Our results demonstrate that the three-tier grouping model can be effectively applied in clinical pathological assessment and has significance for predicting invasion and lymph node metastasis in CRC.

Univariate survival analysis was performed on 237 CRC patients with follow-up data. The analysis revealed that an advanced clinical stage was associated with shorter survival time, and poorer tumor differentiation correlated with reduced survival duration. The group without lymph node metastasis demonstrated longer survival than the group with metastasis. Furthermore, this study identified a significant impact of PI3K p85α protein expression on survival time, with the negative expression group showing longer survival compared to the positive expression group. Multivariate survival analysis further identified clinical stage, tumor differentiation degree, and PI3K p85α protein expression as independent prognostic factors for CRC patients, suggesting their substantial clinical value in prognostic assessment.

This study has several limitations. First, although the data were collected from two independent medical centers, the sample size, while substantial, remains limited. Therefore, our findings warrant further validation in a larger, multicenter cohort to substantiate the roles of PI3K p85α and p53 in the development and progression of CRC. In addition, the retrospective nature of data collection may introduce selection bias. We plan to conduct prospective validation studies in the near future to further enhance the reliability and generalizability of our findings.

Conclusion

This study utilized immunohistochemistry to assess the expression of PI3K p85α and p53 proteins in CRC tissues and adjacent intestinal mucosa. Both PI3K p85α and p53 were significantly overexpressed in CRC tissues compared with paracancerous mucosa. Moreover, PI3K p85α expression was significantly associated with clinical stage, whereas p53 expression correlated with lymph node metastasis. These results indicate that PI3K p85α and p53 may play important roles in CRC pathogenesis and progression. Multivariate analysis further identified PI3K p85α as an independent prognostic factor, highlighting its potential clinical utility in predicting patient outcomes. Future studies should focus on elucidating the underlying molecular mechanisms and validating the prognostic value of these biomarkers in larger, multi-center cohorts.

Data Sharing Statement

The primary data supporting this study's findings are included within the manuscript. Due to hospital regulations and patient privacy considerations, the raw datasets cannot be publicly shared. However, certain anonymized data may be made available for research purposes from the corresponding authors upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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